Autoimmune Disease Control: New Treatments for Old Problems

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Program Overview:
To provide participants with an understanding of autoimmune disease control and new methods being employed.

OBJECTIVES:
After completing this program, participants will be able to:

- Discuss shared symptoms, markers, and disease progression of autoimmune diseases;
- Explain the immune-suppressing mechanisms and risks of belimumab and tolicizumab;
- Describe the appropriate patient who should receive belimumab for treatment of systemic lupus erythematosus (SLE);
- Discuss the etiology of systemic juvenile idiopathic arthritis (SJIA) and the benefits of tolicizumab on the disease symptoms; and
- Identify the symptoms of Restless legs syndrome (RLS), and the benefits of gabapentin enacarbil versus traditional RLS therapies.
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Introduction

Autoimmune diseases affect nearly 24 million Americans and can attack any part of the body, yet they are poorly understood and often inadequately treated. Of the more than 80 types of autoimmune diseases, some attack individual organs and some attack the entire body. Morbidity ranges from quality of life impairment to life-threatening structural organ damage. In addition, numerous chronic health conditions appear to have autoimmune components or are more likely to occur in patients with pre-existing autoimmune diseases. These factors contribute to the complexity of identifying, treating, and managing these conditions for health professionals and patients alike.

Autoimmune Etiologies and Diagnoses

No matter the location of symptoms or the cause of disease activation, the autoimmune etiology remains the same: the body’s attack on a part of itself mistakenly considered a danger. In autoimmune diseases, the body’s acquired immune system, which develops antibodies as necessary to protect the body against invaders, is triggered to build an antibody response to itself. The attack increases white blood cells, specifically T and B cells, which release protein inflammatory factors, such as tumor necrosis factor (TNF), interleukins (ILs), and other cytokines, and the T cell system fails to recognize the improper attack. This multimodal etiology is usually triggered by unknown causes, but it is likely that multiple genetic alterations play a role in turning on the autoimmune disease. Genetic causes alone or in combination with external factors are most probable; common external causes include bacterial infections, UV rays from sunlight, hormonal changes, chemoradiotherapy, and environmental or chemical factors.

Autoimmune diseases are difficult to diagnose, in part because of their mainly nonspecific disease markers and genetic changes that are not yet clearly elucidated. Abnormal blood markers that indicate an inflammatory response can signify possible autoimmune conditions and include the following: increased erythrocyte sedimentation rate (ESR) and decreased red blood cell
(RBC) count, which reflect nonspecific inflammation from an immune attack; positive antinuclear antibody (ANA), which indicates the presence of general autoantibodies; C-reactive protein (CRP), which is made by the liver in response to stress and inflammation and is not normally detectable in the blood; and rheumatoid factor (RF), which differentiates autoimmune from other forms of joint conditions (eg, osteoarthritis) but has poor specificity and sensitivity (ie, numerous false negatives and positives). Each of these markers is most useful for different autoimmune diseases; for example, RF factor increases in rheumatoid arthritis (RA) and Sjogren’s syndrome, but ANA and increased ESR are more common with systemic lupus erythematosus (SLE). An autoimmune diagnosis can be based on markers of inflammation combined with measurements of immune activity (eg, increased white blood cell [WBC] count) and symptoms. Symptoms themselves vary drastically among autoimmune diseases by affected organ systems. Hallmark symptoms of attacks include fever, fatigue, and inflammation. Most autoimmune conditions are chronic and progress in a relapsing/remitting form of symptom flares alternating with quiet periods. Because these diseases comprise lifelong self attack, people diagnosed with one autoimmune disorder can have an increased risk for the development of additional autoimmune diseases, and the propensity may be genetically linked. For example, multiple sclerosis shares genetic components with inflammatory bowel diseases but not with other autoimmune conditions; people with SLE can have a connection to antiphospholipid antibody syndrome or glomerulonephritis; and one-third of children with type 1 diabetes develop an autoimmune thyroid, adrenal, or gut condition in adulthood. Although these disease overlaps complicate diagnoses and disease control, they can also be a starting point for treatment options.4–7

Current Treatment Options2, 8

Treatment options for autoimmune diseases typically begin with symptom control—minimizing pain, inflammation, fatigue, rash, and secondary symptoms of depression, anxiety, or insomnia—to improve quality of life. A large part of disease control is the avoidance of triggers and continuation of preventive care; however, progressive or more severe autoimmune conditions require more complex treatment than occasional anti-inflammatory medications—disease-modifying antirheumatic drugs (DMARDs), antimalarials, corticosteroids, or cytotoxic drugs. As the disease processes become better understood, newer treatments aimed at stopping disease
progression are being developed, and they inhibit the body’s immune response to minimize the inflammatory damage. The immediate goals of immune-suppressing agents extend beyond symptom control to halting disease progression, preventing organ damage, and reducing morbidity and mortality. Examples of immunosuppressants are TNF blockers, IL blockers, and T or B cell inhibitors.

Anti-Inflammatory Agents

Medications that minimize inflammatory reactions without altering the immune system are best used to treat mild symptoms of autoimmune disorders, particularly during active flares. Nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are the two most common classes of drugs for this purpose and are widely used in autoimmune and structural conditions.

NSAIDs, such as ibuprofen and naproxen, reduce pain and swelling and minimize fever. They act primarily on prostaglandins (inflammation mediators) rather than on immune cells. One of the most common adverse effects of short-term use is stomach upset, from mild irritation to significant ulceration. Although NSAIDs may be given long term, benefits may not outweigh the risks of liver dysfunction or the inability to prevent future disease progression.

Prescription corticosteroids are synthesized hormones that mimic naturally occurring glucocorticoids in the body. Glucocorticoids respond to stress reactions in the body to reduce local inflammation and immune reactivity. Corticosteroids, such as prednisone or methylprednisolone, also stop swelling, redness, pain, itching, and allergic reactions. Like NSAIDs, corticosteroids are best used for short-term relief of flares rather than for continuous disease control, in part because they do not stop disease progression. Common adverse effects include bloating or weight gain, blurred vision, dry or thin skin, and headache. Corticosteroids can be prescribed repeatedly, but risks of long-term therapy include adrenal malfunction and impaired bone health, which might require supportive care measures (eg, bisphosphonates).

Disease-Modifying Antirheumatic Drugs (DMARDs): Methotrexate and Antimalarials

Drugs that suppress the rheumatic disease process, or DMARDs, are some of the earliest treatments against disease progression, particularly against joint and skin changes. Methotrexate,
a folate antimetabolite that decreases DNA synthesis, has immune-suppressing activity at high doses but is used as an anti-inflammatory agent at low doses for rheumatoid arthritis, psoriasis, and juvenile idiopathic arthritis. Its mechanism of action at low doses is unclear, despite being a standard treatment with proven success and rapid onset of activity (3 to 6 weeks).

The antimalarial medications hydroxychloroquine and chloroquine are also standard treatments to reduce joint and skin symptoms. Chemically related to quinine and identified in the 1960s as useful pain relievers, antimalarial drugs also reduce inflammation around organ linings. Antimalarials alter cell pH to block immune attacks; they decrease autoantibody levels, WBC proliferation, and the number of cytokines to help induce remission. Antimalarials can be combined with prednisone and other anti-inflammatory agents. Their most common adverse effects are gastrointestinal discomfort, loss of appetite, dry skin, headache, and hair loss. Serious retinal damage is possible with high or prolonged doses and can be irreversible. Use of hydroxychloroquine 5 mg/kg/d or less avoids irreversible retinal damage.⁹

**Biologic Immunosuppressants**

Although anti-inflammatory and disease-modifying drugs can impact the immune symptoms or response, sometimes they are not enough to control progression of moderate or severe autoimmune conditions. Research continues to expand rapidly and has identified numerous biologic immunosuppressants that encompass a broad range of mechanisms to prevent transplantation rejection and subdue autoimmune attacks. Immunosuppressants are long-term or maintenance treatment options for people with poorly controlled or moderate-to-severe symptoms of autoimmune disorders. Immune targets vary by drug class and include B or T cell inhibitors, which reduce the quantity and spread of these white blood cells, and cytokine inhibitors, which prevent the release or function of inflammatory proteins (eg, IL and TNF) released from B and T cells during an immune response.

Examples of agents active against T cell proliferation are leflunomide, tacrolimus, and sirolimus; abatacept inhibits the activation of T cells during an immune response. Infliximab, etanercept, adalimumab, and more TNF antagonists are effective at blocking the overproduction of TNF to lessen chronic inflammatory bone and cartilage damage. The newest antibody products are being
developed against ILs and include anakinra, which blocks IL1, and the first IL6 blocker, tolicizumab. Although IL or TNF blockers can be combined with nonbiologic DMARDs, little is known about the potential adverse effects of combined TNF and IL antagonists. Because biologic immunosuppressants inhibit the body’s ability to fight off foreign invaders indiscriminately, both TNF and IL antagonists are associated with increased risk of infection and numerous contraindications, including avoidance during live vaccine immunizations or active infections. TNF antagonists also are associated with an increased risk of cancer; potentially fatal lymphomas have developed after TNF blocker use in children and teenagers. As research in the biologic medication field expands, long-term safety concerns and optimal dosages will be more clearly elucidated.

**Belimumab for SLE**

SLE, also known simply as lupus, may be one of the most well known autoimmune diseases in women; however, no drug has been approved distinctly for the treatment of lupus in more than 50 years, despite research efforts to understand the disease and its symptoms. Because of erratic identification rates, the range of people in the United States who have been diagnosed with a type of lupus is wide—from 300,000 to 1.5 million. The most likely group of people to receive an SLE diagnosis is women ages 15 to 44 years old. The marker that most often supports a diagnosis of lupus is a positive ANA, although ESR can be high when blood vessel damage is involved.

The primary characteristic symptom of lupus is joint pain, which occurs in 90% of sufferers and is accompanied by swelling and redness. Its onset may be subtle or sudden, and pain can last for hours to months. The joint changes can be unpredictable, though they are mostly limited to the limbs, and pain often worsens during winter months. Joint pain typically develops in the morning and improves until the evening; 90% of patients experience low-grade fever secondary to the joint inflammation. Other common symptoms that accompany joint pain during an active flare include hair loss, fatigue, joint swelling, chest pain, and alopecia; petechia, urticaria, and purpura can occur together at varying degrees as well.
Lupus erythematosus has been differentiated into subtypes, including childhood lupus, drug-induced lupus, and cutaneous lupus, according to symptoms. SLE is the most common subtype and affects multiple body systems, especially the heart, nervous system, joints, and skin. Cutaneous lupus can be subtyped into discoid lupus, subacute cutaneous lupus, and vasculitis lupus and may occur in conjunction with SLE. Lupus flares are quite diverse and can be fatal in severe forms. Vasculitis occurring in the limbs or gastric tract, hemolytic anemia, and thrombocytopenia purpura are all serious blood or vessel conditions that cause organ swelling and damage. Severe lupus can lead to kidney damage, nerve damage, and central nervous system impairment if left untreated.¹⁴

Although skin rash is often considered a defining symptom of lupus, it is not always an identifying marker and differs among subtypes. Skin manifestations occur in 75% of all SLE-diagnosed patients, particularly in patients with discoid and subacute cutaneous lupus. A butterfly-shaped rash, flat or raised, spreading across the nasolabia and distinguished from rosacea by its lack of papules is just one example and is most common in discoid lupus with or without SLE. Rashes occurring elsewhere, including the limbs or trunk, more often develop pustules and occur especially with subacute cutaneous SLE. Photosensitivity is common, and rash is often exacerbated by ultraviolet light exposure. Skin welts, mainly on the legs, are more common with vasculitis SLE and are reflective of blood vessel swelling.¹³

Mild and severe forms of lupus are treated distinctly. Mild symptoms, including fever, arthralgias, headache, and rash, may require very little pharmacologic management; NSAIDs and antimalarial agents are often enough to reduce active flares. For more severe disease, a combination of corticosteroids and cytotoxics, such as azathioprine or cyclophosphamide, are first-line treatment. Oral prednisone 40 to 60 mg daily combined with oral azathioprine 1 to 2.5 mg/kg daily or oral cyclophosphamide 1 to 4 mg/kg daily is used initially to control severe flares. Critical flares in the CNS or kidneys are difficult to control and justify intravenous administration of methylprednisolone and cyclophosphamide.¹¹, ¹³, ¹⁴

Patients with moderate or severe lupus or patients who respond poorly to the first-line treatment have historically had limited options. In March 2011, the US Food and Drug Administration approved a new immunosuppressant designed to treat lupus: belimumab (Benlysta, Human
Genome Sciences, and GlaxoSmithKline), a first-in-class monoclonal antibody. Aimed specifically at adults with autoantibody-positive, non-CNS, non-kidney disease that is uncontrolled despite traditional therapy, Benlysta lowers the number of B cells by reducing the duration of B cell survival and the cellular differentiation of B cells that attack the body. Benlysta has a specific mechanism of action at the natural protein BLyS, which binds B cell receptors when Benlysta is not present. The drug is administered intravenously to reduce disease activity, flare severity, and overall corticosteroid load. Benlysta is dosed as 10 mg/kg every 2 weeks initially and every 4 weeks after the first three doses. Its distribution half-life is approximately 1.75 days, and its terminal half-life approaches 20 days. In clinical trials, Benlysta did not require dosages adjustments for renal or hepatic impairment.

The most common adverse effects, in at least 5% of patients in clinical trials, included fever, nausea, diarrhea, insomnia, pain, sore throat, migraine, and infusion-related skin reactions. Infusion hypersensitivity reactions can be severe enough to require diphenhydramine prophylaxis before Benlysta administration. Because it suppresses immune function, Benlysta is associated with an increased risk of serious infections and should not be administered with other biologic immunosuppressants, with cyclophosphamide, or with live vaccines. Benlysta has been used safely with methotrexate in clinical trials, and more combination therapy options will be discovered as Benlysta post-marketing data are reported.

**Actemra for Rheumatic Autoimmune Conditions**

RA is an immune attack on the joints that affects adults as young as 40 years. RA is characterized by rapid early progression; without treatment, permanent joint changes occur within 10 years of disease onset. RA is identified through a combination of disease markers and clinically observed symptoms. Swan-neck deformities of finger joints are definitive, but joint destruction can occur at any set of joints and can be seen on x-rays. Nonspecific markers that support diagnosis are ANA, CRP, and increased ESR. RF, a somewhat specific disease marker, tests positive only in 70% of patients; false positives occur in 5%, so the test is not a single diagnostic tool. Anti CCP, a test for citrulline antibody, is more accurate and specific for RA, even in early disease stages and with negative RF.
Once thought related to RA, juvenile RA (JRA) is now considered distinct and is more often referred to as juvenile idiopathic arthritis (JIA) because of its unknown cause. JIA occurs in people younger than 16 years of age; nearly 300,000 children in the United States are diagnosed with some types of arthritic disease, and JIA is the primary diagnosis, in 50,000 children. JIA onset is approximately 6 months to 16 years and can begin with redness, warmth, swelling, and pain at joints.\textsuperscript{20}

JIA manifests as one of three subtypes: oligoarticular disease at four or fewer joints with or without eye involvement; polyarticular arthritis at five or more joints, often with nodules; and systemic JIA, affecting the entire body. Systemic JIA (SJIA), also known as Still’s disease, occurs in 10\% to 20\% of JIA and is the rarest and most severe form of JIA. SJIA has the worst prognosis, with a 2\% to 4\% mortality rate, causing one-third of JIA deaths.\textsuperscript{20, 21}

Symptoms of SJIA extend beyond joint changes, which may develop after some less characteristic symptoms. High fever and pallor, particularly in the evening, can be the first sign and can recur for up to 2 weeks. A recurring rash that migrates across the body accompanies the early fever; lymph, spleen, cardiac, or lung swelling develop. Eventually, significant joint swelling, stiffness, and pain progress across the body, not limited to single or parallel joints. Liver swelling, worsened cardiac or pleural swelling, and anemia can occur. Ocular inflammation affecting vision supports an SJIA diagnosis.\textsuperscript{20, 21}

Early diagnosis is key to disease control, especially as the number of affected joints increase with increasing severity and decreasing remission rates. Diagnosis of SJIA is complicated not only by the initially indiscriminate and hidden symptoms but also by the lack of definitive diagnostic tests. Differential diagnoses include Lyme disease and cancer. Bone scans to search for structural changes, joint fluid draws and blood cultures to rule out infections, and bone marrow tests to rule out blood cancers are useful. Autoimmune-specific tests include CBC to confirm increased WBC count and immune activity as well as ESR and RBC reflections of inflammation. RF and ANA positivity are typically used to support adult RA diagnoses, and positive ANA is linked to some pediatric eye manifestations. However, neither is reliably increased in children with systemic disease, and results cannot confirm or rule out an SJIA diagnosis. As with RA, measurement of citrulline antibody (anti-CCP) supports SJIA diagnosis.\textsuperscript{19-21}
Treatments for mild adult RA are directed at reducing symptoms of pain and immobility; the top three goals of SJIA are to halt joint breakdown, reduce pain and swelling, and improve function and quality of life. With effective treatment, remission can be induced in 50% to 75% of patients with SJIA. RA and SJIA disease control relies heavily on physical therapy and exercise, as well as on NSAIDs to reduce joint and organ swelling. Short-term and limited corticosteroid use for supportive inflammation relief may be considered. Treatments against both disease mechanisms are vital to preventing permanent deformity and organ damage, though. Methotrexate provides effective anti-inflammatory action for RA with low doses and works within 3 to 4 weeks, especially when combined with other DMARDs, including hydroxychloroquine and lefunomide. Methotrexate combinations with immunosuppressants, such as the IL1 antagonist anakinra or TNF blockers adalimumab, etanercept, or infliximab, can be first-line treatments of more severe disease. SJIA responds to IL1 and IL6 blockade and to antagonism of the T cell inflammatory process. However, agents specifically designed to halt SJIA progression had been lacking until approval of Actemra (Roche, Genetech) in April 2011 for children as young as 2 years old with SJIA, which directly followed its approval in March 2010 for treatment of complicated or moderate-to-severe RA.17

Actemra is a monoclonal antibody IL-6 receptor antagonist that lowers CRP and other markers of inflammation. It can be administered alone or in combination with the methotrexate and has been tested in single doses with 10-25 mg of methotrexate once weekly. Adult dosages start at 4 mg/kg and can be increased to 8 mg/kg for adequate disease control, administered once every 4 weeks as a 1-hour intravenous infusion; the maximum one-time adult dose is 800 mg. Pediatric dosages are administered every 2 instead of 4 weeks and vary according to patient weight: children less than 30 kg should receive 12 mg/kg, and children 30 kg or greater should receive 8 mg/kg.17

Actemra is available in single-use, preservative-free vials that should be refrigerated (2 to 8 C or 36 to 46 F) before use. Once reconstituted, the solution should be diluted slowly in 50 to 100 mL of 0.9% NaCL and infused alone at room temperature. Serum levels peak 1 hour after infusion, and the half-life ranges from 11 to 13 days. Actemra can induce CYP450 upregulation to normal enzyme levels, which may impact liver metabolism of drugs like omeprazole, warfarin, and theophylline.17
Actemra is associated with mild local and systemic adverse effects in clinical trials, including headache, gastric upset, hypertension, and injection-site skin reactions (eg, redness, irritation). Actemra causes dose-proportional reductions in cell counts that increase the likelihood of infection and bleeding disorders. Severe upper respiratory tract infection was more common with Actemra than with methotrexate or other DMARDs in clinical trials. Increases in liver enzymes (ALT/AST) and lipids are not uncommon, so regular monitoring is recommended during Actemra administration for lipid, cell count, and liver enzyme parameters to identify necessary dose adjustments or discontinuation. Lipid assessments should occur 4-8 weeks after the first dose and every 24 weeks thereafter; cell counts should be assessed every 2-4 weeks as necessary; and liver enzymes should be examined every 4-8 weeks during treatment.17

Doses of concomitant DMARDs should be reduced if liver enzymes increase more than 1-3 times the upper limit of normal; Actemra adult dosages of 8 mg/kg can be reduced to 4 mg/kg for similar laboratory changes. Actemra should be discontinued when the following laboratory parameters are reached: absolute neutrophil count < 500/mL, platelets < 50,000/mL, and ALT/AST greater than 5 times the upper limit of normal (ULN).

Actemra is contraindicated with IL1 antagonists, TNF antagonists, or other monoclonal antibody immunosuppressants because of the increased risk of life-threatening infections, and live vaccines should be avoided near or at the time of Actemra administration. Children in particular should receive all updated immunizations prior to beginning Actemra to avoid an impaired antigen response caused by the IL6 blockade.17

People should not receive tolicizumab if they have an allergy to any vial ingredients, liver problems (indicated by AST/ALT greater than 1.5 times the ULN), or demyelinating diseases. People with active infection or whose blood counts are low (platelets less than 100,000/mL, absolute neutrophil count less than 2,000/mL) also cannot receive tolicizumab because of the risk of severe infectious disease.17

In addition to its approved use for joint-related autoimmune disease, Actemra has the potential to treat genetically related autoimmune disorders. In January 2011, the first genetic marker for natural killer cells that is upregulated in alopecia areata (AA), potentially the most common
autoimmune disease, was identified. The upregulated marker, ULBP3, overlaps with genetic changes seen in RA, celiac, and type 1 diabetes, but not in other autoimmune disorders, even skin disorders; this link distinguishes AA as a systemic, not only skin-related, autoimmune disease.\textsuperscript{22}

AA comprises an immune system attack of the hair follicles to cause patchy, at times progressive hair loss. Although AA is not life threatening, it decreases quality of life. Current treatments involve topical or injectable corticosteroids, irritants, and herbals; topical cyclosporine has shown promising benefits as well. However, no immunosuppressant has received approval for AA treatment. The overlap of genetic disease markers with RA, for example, introduces the possibility of treatment with drugs effective against these diseases, such as Actemra, and provides new goals for drug design research.\textsuperscript{22}

**Horizant for Restless Legs Syndrome\textsuperscript{24-27}**

Restless legs syndrome (RLS), also known as Ekbom’s disease, is becoming more understood but is still difficult to diagnose and treat. It is considered a chronic nervous system or sleep disorder with relapsing/remitting symptoms, though no mechanism of action has been elucidated. Structural blood vessel and nerve changes are not present, but neurotransmitter and CNS changes may play a combined role. RLS appears to have a genetic component\textsuperscript{24}; 25\% to 75\% of diagnosed patients have a family history. RLS affects up to 8\% to 10\% of people—men and women equally—in the United States. Forty percent of occurrences develop in pregnancy and dissipate, and the disease most often begins in middle age.\textsuperscript{24,25} Primary RLS is idiopathic, with no known trigger for onset, and is the most common form. Secondary RLS results from a host of identifiable external causes; although RLS itself has no confirmed autoimmune modality, autoimmune diseases like RA, fibromyalgia, and Sjogren’s syndrome are frequently causes of secondary RLS, along with Lyme disease and iron-deficiency anemia. Triggers are individualized and can initiate an active flare of either RLS subtype. Some of the most common triggers include alcohol, smoking, and fatigue as well as antidepressants (ie, selective serotonin reuptake inhibitors and tricyclic antidepressants), H2 antagonists, beta blockers, and antipsychotics.\textsuperscript{24}
RLS symptoms include uncontrollable itch, crawling, and pins, without pain, in any or all four limbs, and a deep urge to move to relieve the sensations. The symptoms worsen when inactive, at rest, or in prone positions; they are worst at night but may flare during the early morning. Progressive in nature, RLS symptoms range from mild to intolerable; RLS is not life threatening but does impact stress levels, sleep amounts, and quality of life. Eighty percent of sufferers experience involuntary limb movements that relieve symptoms; signs of these movements and their discomfort include restlessness, pacing, rubbing of legs, and daytime sleepiness. Diagnosis is mainly clinical through symptom identification, because laboratory tests are not indicative of RLS. Nerve studies and sleep observation tests can aid in the diagnosis.²⁴

Treatment focuses on relieving symptoms or controlling the causative disease. Drugs that ease symptoms include low-dose opiate pain relievers, anticonvulsants for muscle spasms, benzodiazepines (frequently prescribed to induce sleep), and alpha agonists such as clonidine, which turn off the sensory nerve reaction. Agents that alter neurotransmitters, especially dopamine, can relieve symptoms. Levodopa/carbidopa, a combined dopaminergic drug, and dopamine agonists pergolide and ropinirole decrease crawling sensations. However, dopaminergics are associated with systemic side effects, including motor and nerve function difficulties, so a treatment that does not involve dopamine is often preferred.

Gabapentin enacarbil (Horizant, GlaxoSmithKline, Xenoprot), approved on April 6, 2011, to treat moderate to severe RLS, is a non–dopamine-acting, first-in-class drug aimed at RLS. Unlike the epileptic formulation of gabapentin, Horizant contains gabapentin enacarbil, a prodrug, extended-release tablet with specific absorption patterns. Horizant 600 mg is taken once daily, with food, in the evening, and should not be crushed or chewed. Its nutrient transport mechanism ensures adequate absorption and conversion to active gabapentin at disease-specific plasma concentrations.²⁶,²⁷

Gabapentin enacarbil activity is related to the GABA neurotransmitter actions but does not directly affect GABA; its true mechanism in RLS is unknown. In clinical trials, Horizant appears equally effective in all ages and sexes.²⁶,²⁷
Horizant has no known liver metabolism interactions and is excreted through the kidneys. Horizant doses should be reduced in patients with creatinine clearance of 30 to 59 mL/min: initial doses should be given on days 1 and 3, then every day thereafter. Adverse events, generally dose related, are more likely in patients with renal impairment. The most common adverse events in clinical trials were edema, headache, vertigo, dizziness, sedation, and depression. Less than two percent of patients experience blurred vision and lethargy.\textsuperscript{26,27}

Horizant is unsafe to take while driving because of the sleepiness and dizziness that inhibit reactive ability in the same manner as alcohol or diphenhydramine. This impairment occurs in 10\% or more of people taking Horizant, with an onset of 2 hours and duration of up to 14 hours. Horizant interacts with other drugs that are cleared renally, including cimetidine, to reduce gabapentin clearance 20\% and increase its area under the curve 20\%.\textsuperscript{26,27}

**Conclusion**

Autoimmune disorders are a broad and baffling group of chronic diseases, with treatments that can introduce as many risks as benefits. Patients experiencing nondescript symptoms can remain undiagnosed despite referrals to many specialists for individual symptoms. Identification of autoimmune diseases is crucial to patient well being and disease control, particularly because of the expanding field of immunosuppressive agents designed to stop disease progression. Pharmacists can support patients as they learn to live with chronic autoimmune disorders by selecting the most effective therapy, monitoring appropriate laboratory parameters for side effects and drug interactions, and maintaining open communication with patients about their symptom flares and potential new problems.

**Case Study**

A.G., a woman at your pharmacy who has a history of mild SLE, has had her symptoms controlled with tapered corticosteroids for flares and prescription NSAIDs as needed for joint pain and swelling. Her ANA test was positive at diagnosis. At her most recent doctor’s appointment, she was in the midst of an active flare and had low RBC and symptoms of anemia. When coming to your pharmacy to fill a new corticosteroid prescription, she commented that she forgot to report her increased frequency of flares to her doctor; instead of experiencing worse
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symptoms every 2-3 months, she has been feeling poorly every 3-4 weeks (still limited to fatigue, fever, joint and skin problems) and has not identified any new triggers in her SLE journal. Is she a Benlysta candidate? Why or why not? How should you proceed with her prescription and visit?

Because A.G. has developed progressive symptoms that are not controlled by corticosteroids and NSAIDs, she likely requires additional maintenance therapy to stop her SLE progression. Although a first-line combination with azathioprine or cyclophosphamide is an option, A.G. is also a candidate for Benlysta because of her positive ANA and her lack of CNS or renal involvement so far. At this visit, you can fill her steroid prescription with extra counseling about problems of long-term steroid use and a suggestion of maintaining adequate calcium and vitamin D for bone health. In addition, with A.G.’s permission, you can call her physician to discuss the symptom rates and discuss maintenance therapy. If her physician agrees, she can begin Benlysta treatment provided by your pharmacy through a program with her doctor’s office. You recommend monitoring her first injection reaction for potential prophylaxis and remind the doctor to identify any infection risk before starting treatment.
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